



IN THE UNITED STATES PATENT OFFICE

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#13
JLH
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SUPPLEMENTAL DECLARATION UNDER RULE 1.132

- 1) I am the inventor of record for the captioned patent application. I make this Declaration under 37 Code of Federal Regulations Rule 1.132.
- 2) Bazzano. I have read Bazzano, United States Patent No. 5,183,817. Bazzano teaches that PEG-ethanol mixtures are inert cosmetic carrier vehicles. Bazzano says, at column 19, lines 66-68, that "lotions may be prepared using various forms of alcohols or other solubilizers such as glycols or esters." Bazzano here simply reiterates the conventional wisdom that glycols (such as PEG) ethanol are useful "solubilizers"; that is, as an inert diluent or vehicle, without skin penetration efficacy on their own.
- 3) Bazzano discusses using PEG-ethanol as an inert "vehicle" and as a "placebo." Bazzano at col. 21-24 and claims 23-24. Researchers skilled in the art recognize these terms indicate compounds that have no skin permeability or skin penetration efficacy on their own.

- 4) Bazzano's Example I, at column 24, teaches using PEG-ethanol as the vehicle for topical minoxidil administration. This formulation appears simply to have been copied from that for Pharmacia & Upjohn's formulation for their commercially-available ROGAINE® product, which uses PEG-ethanol as the vehicle.
- 5) Mikulak. I have reviewed the abstract provided by the Examiner. I find it uncontroversial. The abstract appears to describe a test of a new skin penetration agent called TPDS. The abstract uses PEG-ethanol (50:50), apparently as the experimental control, and compares it against TPDS, a "commonly used skin penetration enhancer" and oral administration. This abstract confirms that Mikulak et al. consider PEG-ethanol not a skin penetration agent; if it were, Mikulak would have needed to use a different, inert compound as the experimental control.
- 6) Rajadhyaksha. I have reviewed United States Patent No. 5,482,965. It teaches transdermal drug delivery agents useful for the delivery of drugs through the skin and into the systemic blood circulation. The reference highlights the claimed compounds' systemic safety, such as the systemic safety of the breakdown products.

- 7) This is supported by the examples. Example 32 shows a standard skin-penetration activity assay. The results of Example 32 show that the disclosed compounds do indeed work as exceptional skin permeability enhancers, carrying drug compounds entirely through the tested skin samples. This indicates that the same compounds, if used *in vivo*, would provide excellent drug delivery completely through the skin and into the systemic blood circulation.
- 8) The reference teaches using 5-amino-5-ethyl-2-(3-heptyl)-1,3-dioxane ("A5A") as a skin permeability enhancer. Examples 28-30 disclose using A5A at a 5% concentration. The drugs of Examples 28 and 30 are only used systemically. Thus, I conclude that the 5% A5A concentration used effects systemic delivery of the drugs. Thus, I conclude that Example 29, a progesterone skin patch, effects systemic delivery of progesterone through the skin and into the systemic blood circulation. Example 29 is therefore a birth control skin patch.
- 9) Similarly, Example 18 teaches administering minoxidil using 5% A5A. As mentioned above, the reference teaches 5% A5A is useful for the administration of drugs through the skin into the systemic blood circulation. Example 18 does nothing to

teach how to deliver minoxidil to the level of the hair bulbs, nor how to avoid delivery of the minoxidil into the systemic blood circulation, nor how to avoid cardiovascular side effects of such systemic drug delivery.

- 10) Therefore, nothing in the reference enables the claimed invention. Specifically, nothing enables one of skill in the art to practice "penetration enhancer present in a concentration sufficient to aid said active compound in penetrating the skin surface to a depth of approximately the depth of hair bulbs."

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

W. Roy KNOWLES, M.D.
April 25, 2001

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